REMARKS

Claims 1, and 3-34 are pending, of which claims 11-20 and 27-31 are withdrawn.

Claims 1, 3-10, 21-26 and 32-34 remain rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Maliga *et al.* (WO 01/21768; hereinafter "Maliga") in view of Smith *et al.* (hereinafter "Smith"). Applicants strongly disagree for the reasons already of record and additionally for the following reasons.

Maliga in view of Smith do not teach all the claim limitations.

The Examiner bears the initial burden of establishing *prima facie* obviousness. See *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). To support a *prima facie* conclusion of obviousness, the prior art must disclose or suggest all the limitations of the claimed invention. See *In re Lowry*, 32 F.3d 1579, 1582, 32 USPQ2d 1031, 1034 (Fed. Cir. 1994).

The method disclosed in Maliga is totally different than the claimed method. Maliga teaches a site-specific recombination system to delete a selection marker gene from a transformed plastid genome after a gene of interest has been integrated into the plastid genome thereby regenerating marker free transplastomic plants. In contrast, the present claims relate to a selection method involving introducing a gene of interest "in combination with" a dsRNA, where a marker gene is expressed in the host cell while expression is reduced with the dsRNA. Maliga teaches removal of the marker gene entirely. Maliga does not teach reduction of expression and Maliga does not teach or suggest introducing a gene of interest in combination with a dsRNA as required by the claims.

Smith does not remedy the deficiencies of Maliga. Smith teaches gene silencing using a hairpin structure. Smith does not teach or suggest selection methods, marker genes, introducing a gene of interest, or introducing a gene of interest "in combination with" a dsRNA.

Thus, neither Maliga nor Smith, alone or in combination, teach or suggest introducing a gene of interest "in combination with" a dsRNA or a marker gene being expressed in the host cell while expression is reduced with the dsRNA as required by the claims. Because Maliga and Smith do not teach all the claim limitations, a *prima facie* case of obviousness has not been

established.

Maliga Is Not Combinable with Smith Because Maliga Teaches Away Form the Combination.

It is well established that under 35 U.S.C. § 103 the Examiner must consider the reference as a whole, including portions that teach away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984); see also *KSR*, 127 S. Ct. at 1740; MPEP § 2141.03 (VI). It is improper to combine references where the references teach away from their combination. *See* MPEP § 2145 (X)(D)(2) (citing *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). In addition, the Examiner cannot selectively pick and choose from the disclosed parameters without proper motivation as to a particular selection. The mere fact that a reference may be modified to reflect features of the claimed invention does not make the modification, and hence the claimed invention, obvious unless the prior art suggested the desirability of such modification. *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430 (Fed. Cir. 1990); *In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). "[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. . . it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements ***in the way the claimed new invention does***." See *KSR International Co. v. Teleflex Inc.*, 1741 82 USPQ2d 1385, 1396 (2007) (emphasis added). Thus, it is impermissible to simply engage in a hindsight reconstruction of the claimed invention where the reference itself provides no teaching as to why the applicant's combination would have been obvious. *In re Gorman*, 933 F.2d 982, 987, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

Maliga teaches a method for producing transplastomic plants by using a negative selection marker and deleting this selection marker from the plastome by regenerating marker free transplastomic plants. The deletion of the selectable marker gene is crucial in the method described by Maliga, as stated in numerous passages, for example:

> "However, once transformation is accomplished, maintenance of the marker gene is undesirable." (Maliga, page 2, ll. 21-22).

"Therefore, having plastid markers genes in commercial products is undesirable." (Maliga, page 2, ll. 33-34).

"Removal of the antibiotic resistance marker from the transplastomic plants eliminates the metabolic burden imposed by the expression of the selectable marker gene and should also improve public acceptance of the transgenic crops." (Maliga, page 17 line 34 through page 18 line 3).

Maliga further teaches that although the use of CRE recombinase is exemplified other site-specific recombinases could be used for the "**elimination** of the marker genes." (Maliga, page 18, ll. 9-12). Maliga also teaches that the CRE activity can be introduced by crossing to **eliminate** the marker gene (Maliga, page 31, ll. 20-25). Thus, whether using CRE recombinase or other site-specific recombinases directly or by introduction through crossing, the method taught by Maliga still requires **deleting the marker gene**. Therefore, Maliga teaches one of skill in the art that although there may be several alternatives for introducing site-specific recombinases, all comprise as a mandatory step the deletion of the marker gene. Maliga thus teaches away from using other methods which would not require deletion of the marker gene such as reducing marker gene activity.

Furthermore, Maliga discloses that deletion of the marker gene is necessary to increase customer acceptance. Therefore a market pressure exists to avoid marker genes in transgenic crops. From the teachings of Maliga, one skilled in the art would not be motivated to test the method of the present invention or substitute methods because Maliga teaches that methods leaving the marker gene in the genome would be undesirable. Maliga does not disclose any strategies other than deleting the marker gene from the genome and further teaches that it would be advantageous to delete the marker gene. Based on the teaching of Maliga, one of skill in the art would not be motivated to test methods other than deleting the marker gene. When considering Maliga as a whole, Maliga hence teaches away from any substitution or from combinations with any method that does not also delete the marker gene. Smith teaches gene silencing with a hairpin structure. Thus, the teaching of the need to delete the marker gene in Maliga would teach away from combining with a reference that does not teach deletion of a gene or teaches a way of reducing gene activity as in Smith. Maliga and Smith are not combinable

and do not render the claims obvious for this additional reason.

The Examiner contends that "given the teaching that lacking codA expression can be readily used for a negative selection, it would have been obvious for a person with ordinary skill in the art to choose from a finite number of known methods to reduce or eliminate expression of codA" and it would be obvious to try using hairpin silencing to inhibit expression of the codA gene. Applicants strongly disagree.

First, Applicants note that Maliga discloses "lacking codA" not "lacking codA expression." (Maliga, page 34, ll. 18-20). Further as explained above, when considering Maliga as a whole, the method taught in Maliga for "lacking codA" is by deleting the marker gene, which has also been acknowledged by the Examiner, *i.e.* "the plant seedling and tissues expressing codA gene from E. coli are sensitive to 5FC and seedlings lacking codA (**by deletion** due to expression of site-specific recombinase) could be readily identified by 5FC resistance." (Office Action dated May 31, 2007, p. 13; emphasis added).

Analogous to *Ex parte Whalen II* and as explained above, when considered as a whole, Maliga teaches away from any method other than deleting the marker gene. One skilled in the art would have no reason to modify the method of Maliga in a way that would result in the claimed method from the teaching of Maliga requiring the deletion of the marker gene and that leaving the marker gene in the genome would be undesirable and against market pressures. Further the skilled artisan would not be motivated to test a method other than by deleting the marker gene because Maliga teaches that such methods of leaving the marker gene in the genome would be undesirable. See *Ex parte Whalen II,* 89 U.S.P.Q.2d 1078 (BPAI 2008) (where the Board reversed the Examiner's obviousness rejection when the references taught away from their combination, holding that "when the prior art teaches away from the claimed solution ..., obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition.").

Furthermore, assuming *arguendo* Maliga and Smith were combinable, the combination still does not arrive at the claimed invention, for example, because (1) as explained above, all the

claimed limitations are not taught, and/or (2) as explained in the Amendment and Reply Under 37 CFR § 1.111 dated November 15, 2007, the proposed modification to Maliga suggested by the Examiner requires a "substantial reconstruction and redesign" of elements and changes the principle under which the Maliga construct was designed to operate and would render the modified method of Maliga inoperable (*In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349, 352 (CCPA 1959) (The court reversed the obviousness rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate."). MPEP § 2143.02 VI.

Therefore, Maliga and Smith, alone or in combination, do not render obvious the subject matter of independent claim 1 or the claims dependent therefrom. *See In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988) (holding that if an independent claim is nonobvious then any claim dependent therefrom is nonobvious).

CONCLUSION

For at least the above reasons, Applicants respectfully request withdrawal of the rejections and allowance of the claims. If any outstanding issues remain, the Examiner is invited to telephone the undersigned at the number given below.

This response is filed within the three-month period for response from the mailing of the Office Communication dated November 13, 2008. No fee is believed due. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 12810-00057-US from which the undersigned is authorized to draw.

Respectfully submitted,

By 

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